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Lipoprotein abnormalities as a risk factor for progressive nondiabetic renal disease

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Lipoprotein abnormalities as a risk factor for progressive nondiabetic renal disease. Renal disease is accompanied by characteristic alterations of lipoprotein metabolism, which appear as a consequence of nephrotic syndrome or renal insufficiency and are primarily reflected in an altered apolipoprotein profile rather than elevated plasma lipid levels. Their full characterization requires identification of discrete lipoprotein particles. While nephrotic syndrome results in increased concentrations of both cholesterol- and triglyceride-rich apoB-containing lipoproteins, renal insufficiency is characterized by an accumulation of intact or partially metabolised triglyceride-rich apoB-containing lipoproteins. The dyslipidemia has been discussed as a contributory factor for the progression of renal insufficiency through development of glomerulosclerosis and tubulointerstitial lesions together with accelerated atherosclerosis.

Several experimental studies have shown that hyperlipidemia accelerates renal damage. Lipid-lowering treatment can reduce renal lesions and preserve renal function. The documentation in human nondiabetic progressive renal insufficiency is more limited. We have found that increased concentrations of triglyceride-rich, but not cholesterol-rich, apoB-containing lipoproteins are, associated with a more rapid loss of renal function. The underlying pathophysiological mechanisms for the relation between triglyceride-rich apoB-containing lipoproteins and progression of renal insufficiency are not fully understood. Treatment with hypolipemic drugs may attenuate the renal dyslipidemia, but thus far there have been no reports about controlled clinical trials testing the possible effect of such treatment on the progression of renal insufficiency. In summary, there is evidence to suggest that some specific lipoprotein abnormalities are a risk factor for the progression of renal dysfunction, but the final test of such assumptions still rests on the results of urgently needed controlled intervention studies.

Progression of renal insufficiency results from structural changes in the glomeruli and the interstitial tissues, and is related to the activity of the primary underlying renal disease on one hand and to factors that may result from the renal disease or that may be primarily unrelated to the renal disease on the other [1]. Hypertension and proteinuria are well-documented as risk factors for the accelerated decline in renal function [1, 2]. Certain lipoprotein abnormalities that appear during the course of renal insufficiency may also contribute to the progression of disease [3–5].

Key words: lipoproteins, progressive renal disease, renal failure, apolipoproteins, dyslipidemia.

RENAL DYSLIPOPROTEINEMIA

Nephrotic syndrome and progressive renal failure are accompanied by abnormalities of lipoprotein transport. While the nephrotic syndrome is characteristically associated with elevated plasma lipid levels, the dyslipidemia of progressive renal insufficiency is predominantly reflected in altered concentrations and composition of individual lipoproteins [3, 6]. There are two major classes of circulating lipoproteins characterized and differentiated on the basis of apolipoprotein (apo) composition, one of which contains apoA-I and the other apoB as major protein constituents [7]. The apoA-I-containing lipoproteins occur in high density lipoprotein (HDL) and are considered to be anti-atherogenic, while atherogenic apoB-containing lipoproteins constitute the lipoproteins of very-low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL density ranges. The apoB-containing lipoproteins consist of lipoprotein B (Lp-B) characterized by apoB as the sole protein constituent and lipoprotein B:E (Lp-B:E), lipoprotein B:C (Lp-B:C), lipoprotein B:C:E (Lp-B:C:E) and lipoprotein AII:B:C:D:E (Lp-A-II:B:C:D:E) which, in addition to apoB, contain various amounts of minor apolipoproteins such as apoA-II, apoC, apoD and apoE. The sum of Lp-B:C, Lp-B:C:E and Lp-A-II:B:C:D:E is referred to as lipoprotein B complex (Lp-Bc). While cholesterol esters are the main lipid component of Lp-B, the Lp-Bc particles and Lp-B:E contain triglycerides as the major lipid constituent. The Lp-Bc includes intact and partially metabolised lipoproteins with varying triglyceride content.

The nephrotic syndrome is characterized by increased levels of both cholesterol-rich and triglyceride-rich apoB-containing lipoproteins [6]. The main lipoprotein abnor-

mality of renal insufficiency is a progressive increase of intact and partially delipidized triglyceride-rich apoB-containing lipoproteins, Lp-Bc in IDL and LDL, with smaller change in the levels of cholesterol-rich lipoproteins [3, 8, 9]. There is a progressive decline of apoA-containing lipoproteins with reduced HDL cholesterol levels. The dyslipidemia of renal insufficiency also includes compositional changes in the apoB-containing lipoproteins with a relative enrichment of apoC-III [10]. Finally, lipoprotein(a) levels are frequently elevated in patients with nephrotic syndrome or renal failure [3, 11]. The lipoprotein abnormalities are present in many patients already at the early stages of renal function impairment to become more accentuated in advancing renal failure [3, 10, 12].

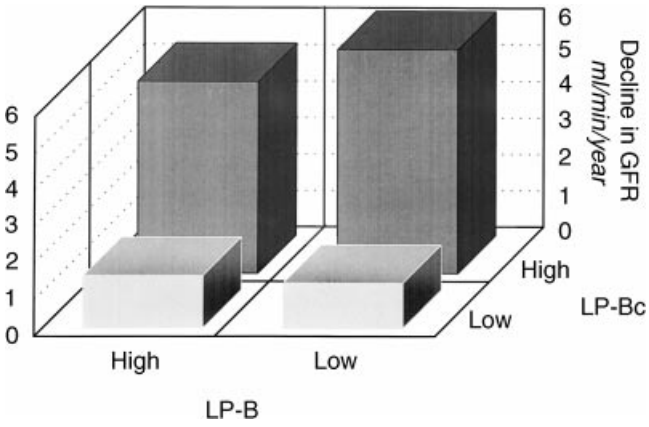

Fig. 1. Rate of decline of renal function in relation to high and low levels of apolipoprotein B (apoB)-containing lipoproteins in 44 patients with primary renal disease. LP-B denotes cholesterol-rich lipoprotein B and LP-Bc triglyceride-rich lipoprotein Bc particles. Cutoff points: median values, 110.0 and 13.5 mg/dl, respectively. (Reproduced with the permission of the Journal of the American Society of Nephrology.)

ROLE OF LIPOPROTEINS IN MECHANISMS OF PROGRESSION

From experimental observations and findings of lipid depositions in diseased kidneys, it has been suggested that circulating lipoproteins may be involved in the development of glomerulosclerosis and tubulointerstitial lesions that lead to a progressive loss of renal function [4, 13, 14]. After a primary insult the damaged glomerular barrier to the mesangium could allow an influx of macromolecules, such as lipoproteins. Through a series of events analogous to the development of atherosclerosis, proliferative and sclerotic processes are triggered, ultimately leading to a partial or complete obliteration of the glomerular capillaries [15]. The glomerular lesions may also lead to a filtration of lipoproteins that may be taken up and induce inflammatory and sclerotic processes in the tubulointerstitial tissue [3, 4, 14].

The experimental evidence suggests that it is the elevated concentration of apoB-containing lipoproteins that contributes to further progression of renal injury [5, 13]. Pharmacological reduction of both cholesterol-rich and triglyceride-rich apoB-containing lipoproteins attenuates the development of experimental glomerular and tubular lesions [14]. It has been suggested that the composition of circulating lipoproteins may be a strong determinant of their nephrotoxic potential and that structurally or functionally altered lipoprotein particles may exert a particularly damaging influence [16].

LIPOPROTEINS AND PROGRESSION OF HUMAN RENAL DISEASE

A number of studies have addressed the relationship between dyslipidemia and progression of renal failure in patients with renal disease. However, only a small number of studies have explored the dyslipidemia beyond measurements of plasma lipids [5, 9, 11, 17–21].

In earlier studies Maschio et al [17] and Capelli et al [18] observed a relationship between elevated concentrations of plasma lipids or an altered relation between apoA- and apoB-containing lipoproteins and the rate of progression. In the MDRD study, low HDL-cholesterol was an independent risk factor for progression in the patient group with better renal function, which indirectly reflects that elevated triglycerides may contribute to progression [2]. In a first study we showed significant correlations between elevated levels of triglycerides, VLDL cholesterol and apoB, respectively, and the rate of progression of renal insufficiency in 34 patients during three years follow-up [20]. Based on these findings we carried out a three-year prospective study of 73 patients with primary renal disease [21]. The decline of renal function, measured with ^{51}Cr-EDTA clearance was significantly associated with the baseline concentrations of apoB and LDL cholesterol. In the 43 patients with chronic glomerulonephritis as the primary renal disease, also elevated levels of triglycerides and apoE were significantly correlated with a more rapid rate of progression. There was, however, no correlation between baseline levels of lipoprotein(a) and the rate of decline of renal function [11].

These observations strongly suggested that one or more of the apoB-containing lipoproteins were risk factors for the progressive loss of renal function. The development of specific sequential immunoaffinity chromatography procedure has provided a tool for analysis of the individual apoB-containing lipoproteins [7]. In our prospective study we could then show that the association between apoB-containing lipoproteins and the progression of renal insufficiency was explained by increased plasma concentrations of triglyceride-rich apoB-containing lipoproteins (Lp-Bc) [9]. In contrast, the impact of elevated plasma concentrations of cholesterol-rich apoB-containing lipoproteins (Lp-B) was only marginal (Fig. 1). These findings may appear to be in conflict with

the observed correlation between LDL-cholesterol and the rate of progression. However, LDL-cholesterol levels, when estimated by the Friedewald formula, include those of IDL cholesterol and the cholesterol content of the majority of the complex apoB-containing lipoprotein particles.

While the above results lend strong support for an association between levels of certain apoB-containing lipoproteins and the rate of progression of renal disease, they do not prove a causality. To this end, intervention studies, designed to show that the reduction of one or more of these lipoproteins also results in a slower rate of progression, are needed but are not yet available. Lipid-lowering intervention studies in nondiabetic patients with nephrotic syndrome have shown that treatment with simvastatin or lovastatin reduces the levels of cholesterol-rich lipoproteins, but have not shown any effect on the progression of renal insufficiency and, at most, only a moderate reduction of proteinuria [3, 5]. There are currently no prospective studies with primarily triglyceride-lowering intervention.

Another line of support for a possible causative role of circulating apoB-containing lipoproteins may be obtained from the analogy between the atherosclerotic processes and the renal lesions [15]. Recent intervention studies have demonstrated that the reduction of both the cholesterol-rich and triglyceride-rich lipoproteins results in an attenuated progression of coronary lesions [22, 23]. The results from our observational studies in renal patients and inference from the intervention studies in coronary artery disease suggest that lipid-lowering intervention against progression of renal disease, should, at least hypothetically, be directed towards lowering of triglyceride-rich lipoproteins.

THERAPEUTIC ASPECTS

Several of the presently available lipid-lowering agents may affect both the cholesterol-rich and the triglyceride-rich apoB-containing lipoproteins in patients with renal disease [3, 24]. In a randomized, controlled treatment study with diet and the second generation fibrate gemfibrozil we found that gemfibrozil treatment lead to a moderate reduction of both types of lipoprotein particles [25]. In another randomized, double-blind placebo controlled study we recently demonstrated that treatment in patients with moderate renal insufficiency with the synthetic statin, fluvastatin, gave a 22% reduction of cholesterol-rich lipoprotein particles (Lp-B) and a 14% reduction of triglyceride-rich lipoprotein particles (Lp-Bc) [26].

In conclusion, studies of human renal disease suggest an association between concentrations of certain circulating apoB-containing lipoproteins and the rate of progression of renal insufficiency. To establish a causative role of these lipoproteins in the progression of kidney dysfunction, we need prospective controlled intervention studies over a sufficiently long period of time. Awaiting those urgently needed studies, the approach to the dyslipidemia of patients with progressive renal disease must be based on circumstantial evidence. They suggest that treatment of the dyslipidemia, in addition to normalization of blood pressure and reduction of proteinuria, could provide additional means to retard the progression of chronic renal insufficiency.

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